UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,338	07/11/2003	Jin-an Jiao	TNA-005.04	8452

25181 7590 01/16/2007

FOLEY HOAG, LLP
PATENT GROUP, WORLD TRADE CENTER WEST
155 SEAPORT BLVD
BOSTON, MA 02110

EXAMINER	
XIE, XIAOZHEN	
ART UNIT	**PAPER NUMBER**
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,338	JIAO ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,39-46,48 and 54-68* is/are pending in the application.

4a) Of the above claim(s) *62-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39-46,48,54-61 and 65-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20061019*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The Information Disclosure Statement (IDS) filed 19 October 2006 has been entered. Applicant's amendments of the specification and the claims received on 18 October 2006 are acknowledged.

Claims 38, 47, and 49-53 are canceled. Claims 65-68 have been added. Claims 37, 39-46, 48 and 54-68 are pending. Claims 62-64 are withdrawn from further consideration as being drawn to a nonelected invention. Claims 37, 39-46, 48 and 54-61 and 65-68 are under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Specification

The objection to the specification for failing to update the cross-references in the first paragraph is withdrawn in response to applicant's amendment of the specification.

Claim Rejections Withdrawn

The rejection of claims 37-61 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, is withdrawn in response to Applicant's amendment and cancellation of the claims.

The rejections of claim 37 under 35 U.S.C. §112, second paragraph, as being indefinite and lack of antecedent basis, are withdrawn in response to Applicant's amendment of the claim.

The rejection of claims 38 and 55-57 under 35 U.S.C. §112, second paragraph, as being lack of antecedent basis for the recitation "the complex", is withdrawn in response to Applicant's amendment and cancellation of the claims.

The rejection of claim 47 under 35 U.S.C. §112, second paragraph, as being indefinite for reciting the polynucleotide sequence of SEQ ID NO: 1 as an amino acid sequence, is withdrawn in response to Applicant's cancellation of the claim.

Claim Rejections Maintained

Claims 37, 39-46, 48 and 54-61 and 65-68 remain rejected under 35 U.S.C. 112, first paragraph, as being lack of full enablement for reducing tissue factor (TF) levels to treat any type of cancer in a mammal for reasons set forth in the previous office action.

Applicant argues that the specification describes the inhibition of TF activity by the H36.D2 antibody in a human bladder carcinoma cell line and detection of TF on the surface of human lung carcinoma and human melanoma tumor cells. Applicant argues that the instant specification provides a sufficient teaching to enable one of ordinary skill in the art to make a variety of antibodies that bind native human TF to form a complex, and means to test the antibodies for anti-cancer activity.

Applicant's arguments have been fully considered but have not been found to be persuasive.

The instant claims encompass treating all forms of cancer. As stated previously, the specification, while being enabling for a method for reducing TF levels to treat a solid tumor that expresses TF, does not reasonably provide enablement for treating all forms of cancer including those without elevated TF expression. Applicant discloses that

an anti-TF antibody/cytotoxin or effector molecule conjugate can be used to treat a mammal having tumor cells that express TF, e.g. breast cancer, lung cancer, pancreatic cancer and ovarian cancer (pp. 20, lines 3-8, and pp. 21, last paragraph). Applicant discloses detection of elevated TF expression on the surface of human lung carcinoma, human melanoma A375-C15 cells and human bladder carcinoma cells as compared to the non-cancerous tissue/cells (Examples 7 and 11). Applicant, however, has not provided support for anti-cancer effect of the antibody for all types of cancer, nor the ubiquitous over-expression of TF on surfaces of all cancer cells. Yamashita et al. (J. Surg. Oncol., 2006) teaches that TF expression has been identified in epithelial tissues, however, a direct correlation between elevated TF expression and advanced stages of malignancy has been reported in several different types of cancers, including non-small cell lung, breast, pancreatic ductal, colorectal, hepatocellular and prostate carcinoma, as well as melanoma (2nd paragraph in Introduction). Without further guidance, the artisan would not be able to predict what types of cancers could be treated using the claimed antibody. The enablement requirement of 35 U.S.C. 112, first paragraph, stipulates one of ordinary skill in the art to make and use the invention, rather than "make and test". Thus, it would require undue experimentation for the artisan to practice the invention as broadly claimed.

Claims 37, 42 and 54-61 remain rejected under 35 U.S.C. 102(b) as being anticipated by Edgington et al. (1993, U. S. Patent NO: 5,223,427) for reasons set forth in the previous office action.

Applicant argues that the '427 patent teaches an anti-TF antibody referred to as TF8-5G9. Applicant argues that the '427 patent does not teach or suggest a method of blocking FX binding to TF wherein TF levels can be reduced in a mammal to treat cancer.

Applicant's arguments have been fully considered but have not been found to be persuasive.

The '427 patent teaches an anti-TF antibody referred to as TF8-11D12 (column 50, Table 8). The TF8-11D12 antibody has an inherent property of inhibiting FX binding to the complex of TF:FVIIa while not inhibiting FVIIa binding to TF (see Fiore et al. in the next paragraph). The '427 patent teaches the inhibitory effects of the antibody to TF activity (column 21, lines 27-30), and teaches administering the antibody to a patient for treating breast and lung carcinoma (column 23, lines 3-11).

While the '427 patent does not explicitly disclose the mechanistic actions of in-vivo bodily activities (i.e, "whereby Factor X binding to the complex is inhibited and Factor VII or VIIa binding to tissue factor is not inhibited"), the patent specifically teaches administering an antibody that binds native human tissue factor. Thus, it would be expected that a "complex" between the prior art's antibody and tissue factor would form inside a patient due to the fact that the antibody is specific for tissue factor. Furthermore, since the product of the prior art is identical to that required by the claims, the method will inherently inhibit Factor X binding to the complex and not inhibit Factor VII or VIIa from binding to the complex. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993). Thus, it does not appear that the claim language or limitation results in a

manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

New Grounds of Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 37, 42 and 54-57 are rejected under 35 U.S.C. 102(b) as being anticipated by Fiore et al. (Blood, 1992, Vol. 80(12):3127-3134).

Fiore teaches a monoclonal anti-TF antibody (TF8-11D12), which does not block binding of FVIIa to TF, however, acts by specifically blocking access of macromolecular substrates, e.g., Factor X, to the formed complex of TF and FVIIa (pp. 3127, Abstract, and last paragraph in Introduction) (claims 37 and 42). Fiore teaches using such antibody for therapeutic interventions of TF-mediated thrombotic disorders, and preclinical studies of this antibody in chimpanzees (i.e., administering to a mammal) have been initiated (pp. 3127, Abstract, and 2nd. paragraph in Introduction) (claim 37). Fiore teaches the Fab fragments (pp. 3128, in Materials and Methods, section "antibodies and Fab fragments") (claim 54). Fiore further teaches that TF8-11D12 IgG abolished formation of FXa by the TF:FVIIa complex (pp. 3131, left column, lines 18-21, and Fig. 4) (claims 55-57). Therefore, Fiore anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 43-46 and 65-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fiore et al., or over U. S. Patent NO: 5,223,427, in view of Queen et al. (1997, U. S. Patent NO: 5,693,762).

Fiore and the '427 patent teach as set forth above. Fiore and the '427 patent, however, do not teach that the antibody is a chimeric (claim 43) or humanized (claim 66) antibody and fragment thereof (claim 67) that comprises a mouse variable region (claim 65) or variable regions of non-human origin (claim 45), and a constant region of human origin (claim 44), nor teach a single chain antibody (claim 46).

The '762 patent teaches chimeric and humanized antibodies that have mouse variable regions joined to human constant regions (column 1, last paragraph). The '762 patent teaches that humanized antibodies are important because they bind to the same antigen as the original antibodies, but are less immunogenic when injected into humans (column 2, lines 6-9). The '762 patent further teaches Fab fragments and single chain antibody (column 17, line 32-44).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Fiore or the '427 patent, with

those of the '762 patent to generate humanized or chimeric anti-TF antibodies and their antigen-binding fragments, or a single chain antibody. One of ordinary skill in the art would have been motivated to combine the teachings, because Fiore and the '427 patent teach monoclonal anti-TF antibodies and the '762 patent teaches modifying monoclonal antibodies for human therapeutic uses. Therefore, the combined teachings provide a reasonable expectation of successfully reducing TF levels to treat tumors that express TF in a patient.

Claim Objections

Claim 43 and 48 is objected to because of the following informalities:

Claim 43 recites "wherein the antibody is chimeric", which should be "wherein the antibody is a chimeric antibody".

Claim 48 recites "the method of claim 47". Claim 47 has been cancelled.

Appropriate correction is required.

Conclusion

NO CLAIM IS ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph. D.
December 29, 2006

GARY B. NICKOL, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600